Growth and long-term development after in utero exposure to coumarins

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Chapter 6

Growth until puberty after in utero exposure to coumarins

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Abstract

Anticoagulation with coumarins is an effective therapy during pregnancy. However, foetal exposure to coumarin derivatives during the first trimester is associated with skeletal anomalies (warfarin or coumarin embryopathy.) Information about long-term effects of prenatal coumarin exposure on the skeletal development is not available. We investigated growth and body proportions at school age of children exposed to coumarins in utero. A blind population-based cohort study was conducted on 307 exposed children and 267 non-exposed controls aged 8-15 years. The exposed cohort was based on a prospective registry of coumarin-treated pregnant women. Anthropometric data included height, weight, head circumference, and measurements to evaluate body proportions.
The mean height of exposed children did not differ from that of the non-exposed children (mean difference 0.01 SD). In addition, no differences were found for the proportional measures. As a group, children exposed in the first trimester showed no evidence of growth impairment. However, two children in this group were born with signs of coumarin embryopathy and one of these displayed a deficit in height at school age. Long-term growth was not affected by a high cumulative dosage or exposure after the first trimester. We conclude that, when exposure during the first trimester is avoided, coumarin therapy during pregnancy has no demonstrable risk for the child's skeletal development.

Key words: coumarin embryopathy, long-term growth, anticoagulants, pregnancy

Introduction

Anticoagulant therapy during pregnancy is indicated for the treatment and prophylaxis of thromboembolic disease and prevention of systemic embolism in patients with valvular heart disease or prosthetic heart valves[1]. The prescription of anticoagulants during pregnancy must be carefully considered because of adverse effects in both mother and child. Heparins have the potential for causing adverse effects in the mother while coumarins (acenocoumarol, phenprocoumon and coumadin/warfarin®) may cause birth defects[2,3]. Centres in Europe often use the protocol which prescribes heparin during the first trimester of gestation and from the 36th week until birth, while coumarins are prescribed during the second and third trimester of pregnancy[4,5]. In the United States, heparin is preferred throughout pregnancy because there is great concern about the teratogenic effect of coumarins[6,7].

Case reports describe central nervous system[8,9] and skeletal abnormalities[10-12] after in utero exposure to coumarins. The bone defects constitute the so-called 'coumarin (or warfarin) embryopathy', while the term 'coumarin syndrome' refers to the central nervous system anomalies. Reported skeletal anomalies observed shortly after birth include various degrees of nasal hypoplasia, rhizomelia, hypoplastic distal phalanges and stippling in epiphyses. There is one report of a prenatally exposed child who showed disturbed growth during childhood resulting in a disproportionally short stature at adult age[13]. In a review of published cases, it was assumed that exposure during the first trimester of pregnancy, especially from the 6th to the 9th week, confers the greatest risk for developing the coumarin embryopathy[14].

Animal studies confirm an effect of warfarin exposure on growth. Rats showed a decreased body length after 12 weeks of postnatal warfarin treatment which was correlated with calcium bridges in epiphyses[15]. Chronic exposure of developing rats caused growth plate closure resulting in cessation of growth[16]. It is not clear whether these findings resemble the skeletal abnormalities seen in humans.

So far, growth at school age has not been examined in children who were prenatally exposed to coumarins. Knowledge of long-term effects for the child's development are essential for a careful consideration of anticoagulant therapy in pregnant women. We performed a large cohort study to assess late effects in children exposed to coumarins in utero. The aim of the present study is to determine whether prenatal exposure to coumarin derivatives causes a (disproportionally) short stature or other growth impairment at school age.

Subjects and Methods

Subjects

Two groups are included in the study: a cohort of children exposed in utero to coumarin derivatives and a cohort of non-exposed controls. The coumarin-exposed children were offspring of mothers included during pregnancy in a registry by Dutch anticoagulation clinics, charged with monitoring oral anticoagulant therapy in out-patients. Inclusion criteria for the exposed study group were: consent for registration, prescription of coumarin derivatives during pregnancy and childbirth between January 1st, 1982 and December 31st, 1990. Eligible registered women were approached by the anticoagulation clinics, either directly or after consultation with the family's general practitioner. Non-exposed control children were approached by regional vaccination centres, keeping records of the inoculation of all children in The Netherlands. Matching was done for age (± ½ year) and sex to obtain an equal distribution in both study cohorts, and for demographic region (postal code) as a measure of socio-economic status. Exclusion criteria were diseases interfering with growth which are not related to coumarin exposure, including Down syndrome.

The study protocol was approved by the Medical Ethics Committee of the University Hospital Groningen and the parents of all children gave written informed consent.

Data collection

After enrolment in the study, all children received an appointment for physical examination. Puberty assessment included examination of secondary sexual characteristics according to Tanner[17]. We considered breast developmentstage 2 in girls and mean testicular volume of 5 ml in boys as minimum criteria for the onset of puberty.

Information about pregnancy, delivery, and the medical history of the child were obtained by questionnaire. We inquired about parental height and weight as references for target height and Body Mass Index of the child. Maternal education and paternal occupation, the latter classified according to Sixma and Ultee[18], were regarded as measures of socio-economic status.

For the exposed cohort, information about indication, period, coumarin derivative, and prescribed dosage during pregnancy was collected from the initial registration form together with medical records from anticoagulation clinics and gynaecologists.

Anthropometric measurements

The anthropometric data were collected by a trained observer who was not aware of the exposure status of the child. Measurements were performed on subjects wearing light clothing (underwear) and repeated three times, measuring to the nearest 0.1 centimetre. Height and sitting height were measured by two observers; for sitting height the child was

placed on a standard stool with his feet on a footrest. Head circumference was measured with a non-stretchable tape at the most prominent points of occiput and forehead. Arm span was measured (with a non-elastic measuring rod) as the distance between the tips of the stretched middle fingers, the child standing with his arms fully extended. The different skeletal parts were measured on the left side of the body using bony prominences as anatomical landmarks. Upper arm length was measured from the lateral border of the acromion to the head of the radius, lower arm length from the head to the bottom of the radius, and hand length from the bottom of the radius to the tip of the longest finger. Biacromial diameter was measured between the lateral borders of the acromion processes and biiliacal diameter at the widest point of the iliac crests, using the anterior superior spina iliaca as a landmark. The distance from the proximal medial border of the tibia to the distal border of the medial malleolus was used for tibia length; the distance between the most posterior part of the heel and the tip of the longest toe was used for the foot length. Weight was measured in kilograms, using a digital scale with an accuracy of 100 grams.

Statistical analysis

To adjust for sex and age, we calculated SD-scores using Dutch references[19]. Values were expressed in means ± standard deviation. For the comparison of weight, Body Mass Index (kg/m^2) was calculated. Statistical differences between exposed and non-exposed children were assessed by linear regression analysis, controlling for the confounding variables sex, age, target height, puberty, and socio-economic status.

Exposure to coumarins was classified according to trimester (exposure at least during the first trimester of pregnancy or exposure only during the second or third trimester), derivative (acenocoumarol or phenprocoumon), and daily dosage. In addition, cumulative dosage (duration (days) calculated from start and stop date of therapy multiplied by mean daily dosage) was used to investigate the combined effect of dosage and duration of exposure. In order to disentangle the effect of coumarin exposure from the effect of maternal disease, we performed a stratified analysis by indication for coumarin treatment during pregnancy. The significance level was set at $p<0.05$. Statistical analysis was performed with SPSS[20].

Results

Study population

A total of 574 children were enrolled in the study, 307 in the exposed and 267 in the non-exposed cohort, respectively. For the exposed cohort, 451 pregnancies registered by Dutch anticoagulation clinics were considered for inclusion. Fifty-five of these women could not be traced because of incomplete personal data. Of 14 families, the general practitioner

discouraged contact because of death or severe illness of the mother (n=6) or because of other familial circumstances (n=5). In three cases, the general practitioner did not give an explication, but the child concerned was healthy. The remaining 382 registered pregnancies proved eligible for inclusion; 307 of these children actually participated in the study (response rate 80%). In 75 cases, participation was refused because the child was not willing to cooperate (n=15), the mother had no contact with the child because of divorce (n=6), 'taking part costed too much time' (n=8), or participation in the planned investigation period was not possible due to familial circumstances (n=4). Forty-three parents declined participation without explanation.

Characteristics of the exposed and non-exposed cohort are presented in Table 1. Gestational age was lower in the exposed study cohort probably related to a higher percentage of labour induction in this high risk group (31% vs. 12%, RR=2.5 CI_{95} 1.7 to 3.5). Birth weight and

Table 1. Characteristics of study population

	Exposed	Non-exposed
Number of patients	307	267
Gender: male	50%	53%
Caucasian origin	93%	93%
Gestational age (wks)	38.9 (±2.0)*	39.4 (±1.8)*
Birthweight (grams)	3229 (±577)	3380 (±598)
Length at birth (cm)	49.7 (±3.0)	50.2 (±2.8)
Mean age in yrs (sd)	10.7 (±2.0)	10.5 (±2.0)
Puberty:		
prepubertal	165 (54%)	161 (60%)
pubertal	120 (39%)	85 (32%)
unknown	22 (7%)	21 (8%)
Socio-economic status:		
- Education mother		
untrained	4 (1%)	3 (1%)
low	137 (45%)	118 (44%)
middle	108 (35%)	92 (34%)
high	55 (18%)	53 (20%)
- Occupation father		
unknown/single parent	14 (5%)	18 (7%)
none	16 (5%)	10 (4%)
low	78 (25%)	69 (26%)
middle	129 (42%)	108 (40%)
high	70 (23%)	62 (23%)

p=0.01, Mann Whitney U test

length, when adjusted for gestational age, were not significantly different. Age at study was similar in both groups ranging from 7.6 to 15.3 years. Mean age at the various stages of puberty, both in boys and in girls, were not significantly different for the exposed and non-exposed cohort. For four children (three exposed, one non-exposed) the level of maternal education could not be identified.

Exposure

Indications for coumarin derivatives during pregnancy were treatment (n=64) and prophylaxis (n=207) of thromboembolic events, hereditary thrombophilia (n=11), artificial heart valve (n=10), and a group of incidental causes like antiphospholipid antibody syndrome, trauma, and surgery (n=9); for six cases the indication was unknown.

Coumarin derivative and exposure period during pregnancy could be identified for 281 children (92%). Most children (n=240) were exposed during the second or third trimester of pregnancy. The first trimester study group was comprised of 41 children, of which 20 were exposed during (part of) the teratogenic window (6th to 9th gestational week). The duration of exposure ranged from one to 36 weeks (mean: 16 weeks). In most cases (n=239) the short-acting coumarin derivative acenocoumarol was prescribed, while 33 mothers used phenprocoumon. Seven women changed coumarin derivative during pregnancy and in two cases preparation could not be retrieved.

The prescribed dosage during pregnancy was available for 166 subjects (54%) of the exposed cohort. Mean daily dosage was 3.3 mg (± 1.14) for the group exposed to acenocoumarol and

Table 2. Mean SD-score (standard deviation) of growth parameters for coumarin-exposed and non-exposed children

	Exposed n = 307	Non-exposed n = 267	difference*	CI_{95}
height	0.20 (1.0)	0.09 (0.98)	0,01	-0.14 to 0.14
sitting height	0.07 (1.1)	-0.01 (0.99)	-0,01	-0.16 to 0.14
sitting height / height	-0.44 (1.1)	-0.48 (0.98)	0,05	-0.14 to 0.23
head circumference	0.05 (1.1)	-0.07 (0.98)	0,03	-0.14 to 0.20
arm span	0.17 (1.1)	0.06 (1.0)	0,03	-0.13 to 0.18
upper arm length	-0.26 (1.1)	-0.34 (1.1)	<-0.01	-0.17 to 0.16
lower arm length	1.17 (1.3)	1.04 (1.3)	0,1	-0.11 to 0.30
hand length	-0.37 (1.1)	-0.55 (0.96)	0,05	-0.12 to 0.23
biacromial diameter	0.43 (1.2)	0.33 (1.2)	0,08	-0.12 to 0.28
biiliacal diameter	0.73 (1.5)	0.67 (1.4)	-0,04	-0.27 to 0.20
tibia length	0.20 (1.2)	0.14 (1.1)	<0.01	-0.18 to 0.18
foot length	0.20 (1.1)	0.08 (1.0)	0,05	-0.11 to 0.22

*mean difference derived from linear regression analysis comparing exposed versus non-exposed children

3.3 mg (±1.20) for the group exposed to phenprocoumon, respectively. Mean cumulative dosage including both derivatives was 408.7 ± 231.2 mg (range: 34.1 to 1501.0 mg).

Growth

The mean and standard deviation of the calculated SD-scores of height, sitting height, the proportional measure sitting height/height and the other growth parameters of exposed children and non-exposed controls are shown in Table 2. Using linear regression analysis, we found no differences for these parameters between both groups. Body Mass Index was not different between the exposed and non-exposed cohort (mean difference = -0.01, CI_{95} -0.42 to 0.41). Children exposed during the first trimester of pregnancy showed no difference in height compared with children exposed during the second or third trimester and compared with non-exposed controls (Fig. 1).

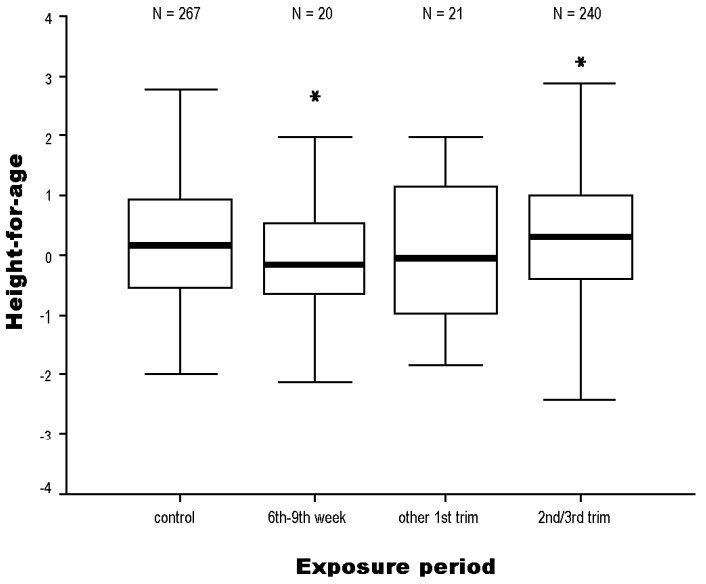

Figure 1. Boxplot of the SD-score height-for-age for non-exposed and coumarin-exposed children in the different exposure periods during pregnancy

Two children exposed during part of the teratogenic window (6th to 9th gestational week) were born with signs of coumarin embryopathy. One of these children was born at 32 weeks, manifesting severe growth retardation (SD-score of birth length -3.78 and SD-score of birthweight -1.73; both corrected for gestational age). At the time of study, this 11-year-old girl displayed a short stature (SD-score of height-for-age: -1,96; SD-score corrected for target height: -2.79) with relatively short legs (SD-score of sitting height/height: 1.43). The other

child was born at 41 weeks with a normal birth length (SD-score corrected for gestational age: 1.56). At 13 years of age, he displayed a normal stature (SD-score of height-for-age: 2.65; SD-score corrected for target height: 1.52), with relatively long legs (SD-score of sitting height/height: -1.15). Fig. 2 shows that there is no relationship between cumulative dosage of in utero exposure to coumarin derivatives and height at school age. Using linear regression analysis, we found that prescribed preparation of coumarin therapy did not have an influence on long-term height (mean difference (d) <-0.001 SD for each mg of acenocoumarol and d< 0.001 SD for each mg phenprocoumon). Stratified analysis showed no differences in height between children whose mothers were treated for acute thromboembolism (d= 0.17, CI_{95} -0.08 to 0.43), prophylaxis of thromboembolism (d= -0.06, CI_{95} -0.22 to 0.11), artificial heart valve (d= 0.45, CI_{95} -0.15 to 1.04), or hereditary thrombophilia (d= 0.22, CI_{95} -0.34 to 0.78) compared with non-exposed control children.

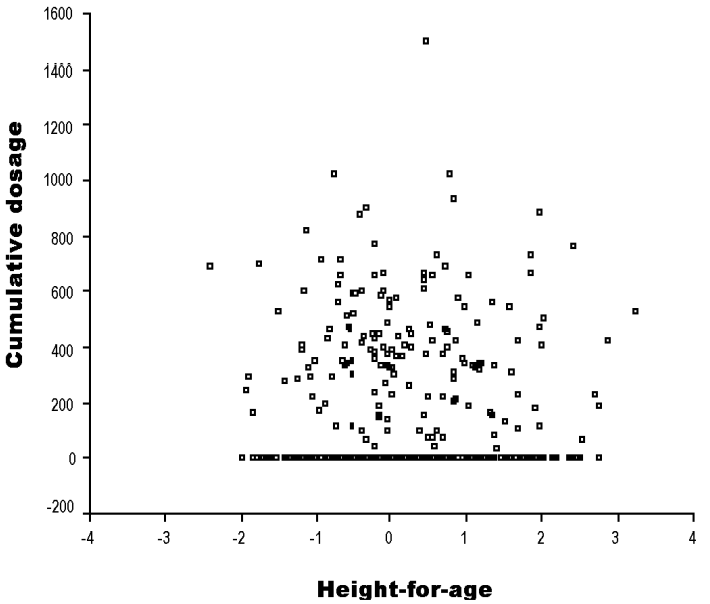

Figure 2. Scatterplot of the SD-score height-for-age versus cumulative dosage of coumarins during pregnancy comparing non-exposed (cum. dosage 0 mg) and coumarin-exposed (cum. dosage 34.1 to 1501.0 mg) children.

Discussion

Our study demonstrates that children exposed to coumarins during pregnancy who are born without signs of coumarin embryopathy do not differ in growth with age-matched non-exposed controls. At school age, we found no differences in various growth parameters and body proportions between children exposed in utero to the coumarins acenocoumarol or phenprocoumon and non-exposed controls. In addition, time of onset of puberty did not differ between the exposed and non-exposed children. On the other hand, we found two children who were exposed to coumarins in the first trimester of pregnancy and were born with manifestations of coumarin embryopathy. One of these children was growth retarded at school age.

One of the hypotheses about the pathogenesis of coumarin embryopathy proposes a decreased production of Vitamin K-dependent mineralisation inhibitors in cartilage resulting in ectopic calcium deposits in epiphyses and nasal septum. Experiments in rats showed maxillonasal hypoplasia together with ectopic calcium deposits in the septal cartilage of the nasal septum and in epiphyseal growth plates after warfarin treatment[15]. Another theory states that warfarin inhibits the activity of a novel gene, arylsulphatase E, which is assumed to play an important role in the metabolic pathway of some types of chondrodysplasia punctata[21].

Exposure to coumarin derivatives during the first trimester of gestation, especially from the 6th to the 9th week, carries the greatest risk for inducing skeletal anomalies. Signs of coumarin embryopathy are described in association with exposure to warfarin as well as acenocoumarol and phenprocoumon[22-24]; reported prevalence rates vary considerably from 0 to 68%[25-27]. In one case report, an adult with a disproportionate short stature was described after exposure to phenprocoumon during the first trimester[13]. In our study, 41 children were exposed during the first trimester of gestation; 20 of these were exposed during (part of) the proposed teratogenic window. Two of the children who were exposed during the critical period, were born with signs of coumarin embryopathy. This suggests a prevalence rate of 10%. Most children (n=38) were exposed to acenocoumarol, while three were exposed to phenprocoumon. One child exposed in the critical period was born with signs of classic coumarin embryopathy (nasal hypoplasia and stippled epiphyses) which was diagnosed neonatally. Another child who was also exposed during the teratogenic window showed manifestations (nasal hypoplasia with breathing problems) after birth which retrospectively suggested an embryopathy. As a group, children exposed in the first trimester showed no evidence of long-term growth impairment. However, the child with classic coumarin embryopathy showed a short stature with relatively short legs at the time of study. This child, born to a mother suffering from systemic lupus erythematosus, displayed severe growth retardation (-3.78 sds) at birth. Although it is difficult to rule out other influences, the

coumarin exposure may have caused the intrauterine growth retardation, as well as the subsequent growth impairment. The other child with signs of embryopathy at birth showed a normal proportional stature at the time of study. The children in our study who were exposed in the first trimester and were born without overt manifestations of embryopathy had a normal growth at school age.

The vast majority of our study population was exposed during the second and third trimester of pregnancy. We found no evidence that a high cumulative dosage of prenatal exposure to coumarin derivatives has an effect on growth at school age. The mothers of these exposed children used either acenocoumarol or phenprocoumon during pregnancy, with a mean daily dosage of 3.3 mg. Warfarin-treated postnatal rats showed a decreased growth which was related to the exposure duration[15,16]. In these experiments, the rats were treated with warfarin in high dosages ranging from 77 to 100 mg/kg body weight. Differences in dosage and pharmocokinetics may explain the different outcome of our study compared with those in the rat experiments.

Chong et al[28] performed a follow-up study to assess the growth and development of coumarin-exposed children compared with non-exposed controls at 4 years of age. They found no differences in centile distribution of height between the two study groups. This study was small (n=22) and no correction for target height was made.

The exposed cohort of our study was based upon a prospective registry of women treated with coumarins during pregnancy. The response rate of parents and children that were approached was high (80%). Of the 75 parents who refused to participate in the study, in 32 cases the reason not to participate was not related to the condition of the child. In 43 cases, parents refused to cooperate without an explication. Due to privacy reasons, it was not possible to inquire about the reasons to decline. Taking part in the study was time consuming; the investigation was carried out during office hours and lasted for one hour and a half. Since refusal without explication regarded only 11% of the approached parents and children (n=382), the possibility of selection bias is unlikely.

The present study is the first large cohort study to date which investigates growth at school age in children who were prenatally exposed to coumarins. We found that exposure to the coumarin derivatives acenocoumarol and phenprocoumon during the second or third trimester of pregnancy has no effect on growth at school age. This implies that coumarin therapy during pregnancy that adheres to a protocol which avoids treatment during the first trimester has no demonstrable risk for the skeletal growth of the exposed child.

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